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PCT/KR2004/001518

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4FPO-04-07	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. **PCT/KR2004/001518**	International filing date *(day/month/year)* **23 JUNE 2004 (23.06.2004)**	Priority date *(day/month/year)* 25 JUNE 2003 (25.06.2003)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07C 317/30, A61K31/16

Applicant

JE IL PHARMACEUTICAL CO., LTD. et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ (sent to the applicant and to the International Bureau) a total of 9 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
25 JANUARY 2005 (25.01.2005)	17 OCTOBER 2005 (17.10.2005)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer LEE, Suk Ju Telephone No. 82-42-481-8149

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/001518

Box No. I Basis of the report

1. With regard to the **language,** this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☒ This report is based on translations from the original language into the following language English, which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☒ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this reort as "originally filed" and are not annexed to this report):*

   ☐ the international application as originally filed/furnished

   ☒ the description:
   pages 1-151 as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☒ the claims:
   pages _____ as originally filed/furnished
   pages* _____ as amended (together with any statment) under Article 19
   pages* 152-166 received by this Authority on 25.01.2005
   pages* 152-160 received by this Authority on 31.08.2005

   ☒ the drawings:
   pages 1/6-6/6 as originally filed/furnished
   pages* _____ received by this Authority on _____
   pages* _____ received by this Authority on _____

   ☐ the sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:
   ☐ the description, pages _____
   ☒ the claims, Nos. 2
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)* : _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   ☐ the description, pages _____
   ☐ the claims, Nos. _____
   ☐ the drawings, sheets _____
   ☐ the sequence listing *(specify)*: _____
   ☐ any table(s) related to sequence listing *(specify)* : _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/001518

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 3-6	YES
	Claims	None	NO
Inventive step (IS)	Claims	1, 3-6	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1, 3-6	YES
	Claims	None	NO

2. Citations and explanations (Rule 70.7)

I . Reference is made to the following documents:

D1: WO 02/100824 A1

D2: Guan, Jian et al., "Antitumor Agents. 185. Synthesis and Biological Evaluation of Tridemethylthiocolchicine Analogs as Novel Topoisomerase II Inhibitors", Journal of Medicinal Chemistry, 1998, 41(11), 1956-1961

D3: Sun, Li et al., "Antitumor agents. 141. Synthesis and biological evaluation of novel thiocolchicine analogs: N-acyl, N-aroyl-, and N-(substituted benzyl)deacetylthiocolchicines as potent cytotoxic and antimitotic compounds", Journal of Medicinal Chemistry, 1993, 36(10), 1474-9

II . Novelty

Claims 1,3-6 of the present invention relate to a compound represented by a formula 1, a salt thereof, a method of manufacturing the same and an anticancer agent containing the same. None of the prior art documents discloses the compound of the formula 1 wherein B1 is (b) or (c); when B1 is (a), R3 is ethyl, and R6 is hydrogen; or when B1 is (a), halogen and OH(hydroxy) or halogen and -ONO2 substitute for phenyl group at the same time. Thus claims 1,3-6 of the present invention are novel.

III. Inventive Step

Claim 1 discloses the compound wherein when B1 is (a), R3 is ethyl, and R6 is hydrogen; or halogen and OH(hydroxy) or halogen and -ONO2 substitute for phenyl group at the same time. The present invention is different from D1-D3 in that -ONO2 substitutes for phenyl in the compound of D1, OH substitutes for phenyl in the compound of D2, and halogen singularly substitutes for phenyl in D1-D3.

(Countinued on Supplement Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

(BOX V)

To replace by two substituents at the same time cannot be easily invented from the prior art. Concerning the effect in decreasing toxicity of the compound, LD50 and ED50 are remarkable over that of D1-D3. Claim 1 is inventive and claims 3-6 dependent on claim 1 are also inventive.

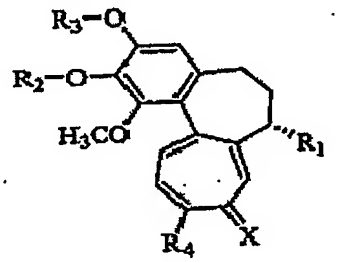
Therefore, claims 1,3-6 of the present invention are considered to meet the requirements of Article 33(3) PCT.

IV. Industrial Applicability

The subject matter of claims 1,3-6 is considered to be industrially applicable under PCT Article 33(4).

What is claimed is

1. **(amended)** A tricyclic derivative represented by the following <Formula 1> or pharmaceutically acceptable salts thereof. <Formula 1>

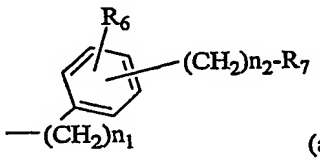


Wherein,

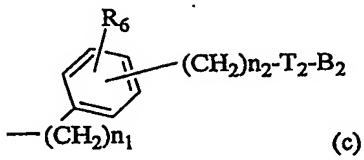
(1) R_1 is $-T_1-B_1$;

in which T_1 is $-N(R_5)C(O)-$, in that R_5 is H or C_1~C_5 alkyl group; and

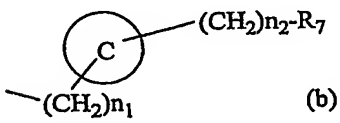
B_1 is selected from a group consisting of following (a)~(c);



(a)

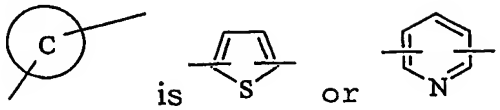


(c)



(b)

wherein,



R_6 is H or halogen;

R_7 is hydroxy or $-ONO_2$ group, with the proviso that when R_6 is H, R_7 is $-ONO_2$ group;

T_2 is -O-C(O)-;

B_2 is said (a) or $-(CH_2)n_3-R_7$;

n_1 is an integer of 0~1;

n_2 is an integer of 0~5; and

n_3 is an integer of 2~5;

(2) R_2 is CH_3;

(3) R_3 is C_1~C_4 straight-chain or branched-chain alkyl or C_3~C_7 cycloalkyl, with the proviso that when B_1 is (a) and R_6 is H, R_3 is C_2H_5 ;

2. (deleted)

3. (amended) The tricyclic derivative or

pharmaceutically acceptable salts thereof as set forth in claim 1, wherein the tricyclic derivative is selected from the group consisting of:

1) 6-nitrooxymethyl-N-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-nicotineamide;

4) N-[(7S)-3-ethoxy-1,2-dimethoxy-10-methyl-sulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-3-nitrooxymethyl-benzamide;

5) 6-nitrooxymethyl-pyridine-2-carboxylic acid-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-amide;

6) 5-nitrooxymethyl-thiophene-2-carboxylic acid-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-amide;

8) N-[(7S)-3-ethoxy-1,2-dimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-2-fluoro-3-nitrooxymethyl-benzamide;

9) 2-fluoro-N-[(7S)-3-isopropoxy-1,2-dimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-3-nitrooxymethyl-benzamide;

10) 2-fluoro-3-nitrooxymethyl-N-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-benzamide;

12) 3-fluoro-5-nitrooxymethyl-N-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-benzamide;

13) N-[(7S)-3-ethoxy-1,2-dimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-3-fluoro-5-nitrooxymethyl-benzamide;

14) 3-fluoro-N-[(7S)-3-isopropoxy-1,2-dimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-5-nitrooxymethyl-benzamide;

15) N-[(7S)-3-cyclopentyloxy-1,2-dimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-3-fluoro-5-nitrooxymethyl-benzamide;

17) 2-fluoro-5-nitrooxymethyl-N-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-benzamide;

21) 4-nitrooxymethyl-thiophene-2-carboxylic acid [(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-amide;

22) 3-nitrooxymethyl-thiophene-2-carboxylic acid [(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl]-amide;

29) 3-nitrooxymethyl-benzoic acid-2-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl-carbamoyl]-phenylester;

30) 4-nitrooxybutyric acid-2-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl-carbamoyl]-phenylester;

31) 3-nitrooxymethyl-benzoic acid-3-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl-carbamoyl]-phenylester;

32) 4-nitrooxybutyric acid-3-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl-carbamoyl]-phenylester;

33) 3-nitrooxymethyl-benzoic acid-3-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl-carbamoyl]-benzylester;

34) 4-nitrooxybutyric acid-3-[(7S)-1,2,3-trimethoxy-10-methylsulfanyl-9-oxo-5,6,7,9-tetrahydro-benzo[a]heptalen-7-yl-carbamoyl]-benzylester;

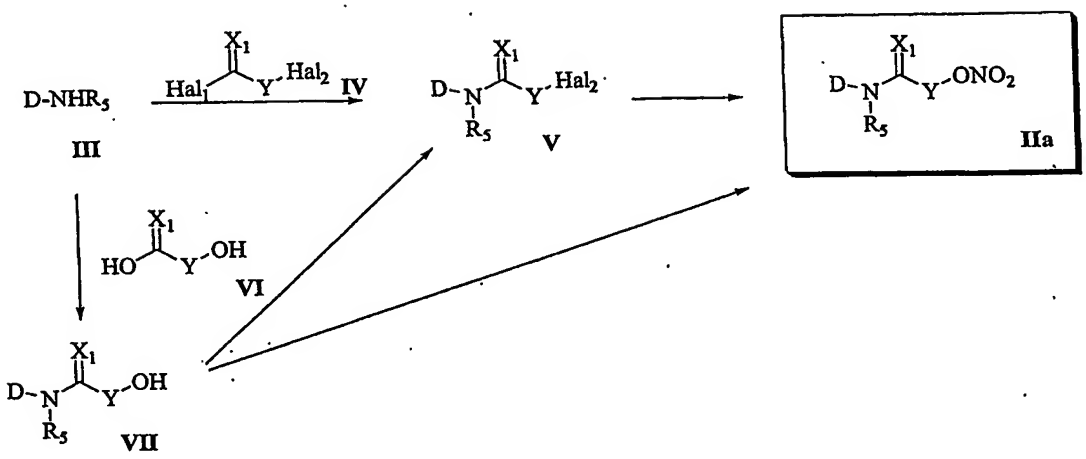
4. (amended) A method for preparing tricyclic derivatives as represented in <Scheme 1> comprising the following steps:

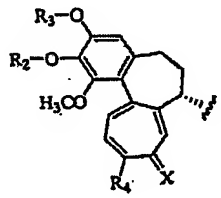
(1) Reaction of the compound of formula (III) with the compound formula (IV) or the compound of formula (VI) is performed to give the compound of formula (V) or the compound of formula (VII), or reaction of the resultant compound of formula (VII) with the halogen compound is performed to give the compound of formula (V) (Step 1); and

(2) Nitration or nitrosation of the prepared compound of formula (V) or the compound of formula

(VII) is performed to give the compound of formula (IIa) (Step 2).

<Scheme 1>





(Wherein, D is , and R_2, R_3, R_4 and X are same as defined in the <Formula 1> of claim 1;

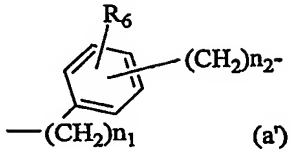
R_5 is H or C_1~C_5 alkyl group;

X_1 is O;

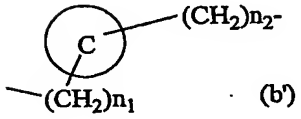
Hal_1 and Hal_2 are halogens;

Hal_1 and Hal_2 of formula (IV) are each same or different halogens, for example F, Cl, Br or I; Y

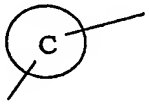
is selected from the group consisting of formula (a') and (b'),



(a')



(b')

wherein, 

, R_6, n_1, and n_2 are same as defined in the <Formula 1> of claim 1.)

5. (amended) An anticancer agent or anti-proliferation agent containing a tricyclic derivative of claim 1 or claim 3 or pharmaceutically acceptable salts thereof as an effective ingredient.

6. (amended) An angiogenesis inhibitor containing a tricyclic derivative of claim 1 or claim 3 or pharmaceutically acceptable salts thereof as an effective ingredient.

(deleted)